UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/580,248	07/20/2006	Mimi Adachi	64517.000003	6084

21967 7590 01/28/2008

HUNTON & WILLIAMS LLP
INTELLECTUAL PROPERTY DEPARTMENT
1900 K STREET, N.W.
SUITE 1200
WASHINGTON, DC 20006-1109

EXAMINER	
SGAGIAS, MAGDALENE K	

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
01/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,248	ADACHI ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *3,13,14,26-30,32 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 4-12, 15-25, 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments with respect to claims 1-2, 4-12, 15-25, 31 have been considered.

Claims 1-33 are pending. Claims 3, 13-14, 26-30, 32-33 are withdrawn. Claims 1-2, 4-12, 15-25, 31 are under consideration.

Claim Objections

Claim 1 is objected under 37 CFR 1.75 as being a substantial duplicate of claim 2. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 4-8, 15-21 and 31 rejection under 35 U.S.C. 103(a) as being unpatentable over Tamamori-Adachi et al, [Circ Res, 92:e12-e19, 2003) in view of Poolman et al, (Circ Res, 85: 117-127, 1999) is withdrawn.

Claims 9-12, 22-25 rejection under 35 U.S.C. 103(a) as being unpatentable over Tamamori-Adachi et al, (Circ Res, 92:e12-e19, 2003) in view of Poolman et al, (Circ Res, 85:

117-127, 1999) as applied to claims 1-2, 4-8, 15-21 and 31 above, and further in view of Tsvetkov et al, (Current Biology, 9: 661-664, 1999); Yu et al, (PNAS, 95: 11324-11329, 1998) is withdrawn.

Claims **1-2, 4-12, 15-25, 31** are rejection under 35 U.S.C. 103(a) as being unpatentable over over **Tamamori-Adachi et al,** [Circ Res, 92:e12-e19, 2003 (IDS)] taken with **Sutterluty et al,** (Nature Cell Biology, 1: 207-214, 1999); **Sherr et al,** [Genes & Development, 13: 1501-1512, 1999, (IDS)]; **Flink et al,** [J Mol Cell Cardiol, 30: 563-578, 1998 (IDS)]; and **Poolman et al,** [Circ Res, 85: 117-127, 1999 (IDS)].

Tamamori-Adachi et al teach co-expression of cyclin D1 and cyclin-dependent kinase 4 (CDK4) by using an adenovirus containing cyclin D1 which directly linked to nuclear localization signal (Ad-D1NLS) to target the cyclin into the nucleus and an adenovirus containing the cyclin-dependent kinase CDK4 (Ad-CDK4) promoted the proliferation of rat neonatal cardiomyocytes in culture (p 6, 2nd column bridge p 7, 1st column, p 7 2nd column, 2nd paragraph). Tamamori-Adachi el also teach Ad-D1NLS/ Ad-CDK4 promoted cell cycle re-entry of adult cardiomyocytes, in situ, in adult hearts injected with these viruses (p 6, 2nd column bridge p 7, 1st column, p 7 2nd column, 2nd paragraph). Tamamori-Adachi et al suggest that postmitotic cardiomyocytes have the potential to proliferate provided that cyclin D1/CDK4 accumulate in the nucleus, and the prevention of their nuclear import plays a critical role as a physical barrier to prevent cardiomyocyte proliferation (abstract). Tamamori-Adachi et al suggest that the nucleocytoplasmic transport machinery of cyclin D1 plays a critical role for determining proliferative capacity of cardiomyocytes however, the precise mechanism preventing cyclin D1 nuclear accumulation remains unclear. Tamamori et al discuss that experiments using transgenic mice carrying wild-type cyclin D1 driven by a-cardiac myosin

heavy chain (MHC) promoter have shown that deregulated wild-type cyclin D1 expression causes an increase in cardiomyocyte number and cardiomyocyte DNA synthesis in the adult heart, however, transient expression of cyclin D1 did not promote cell cycle progression in both neonatal and adult cardiomyocytes (p 7, 2nd column). Tamamori-Adachi et al suggest investigation of the molecular mechanism preventing cyclin D1 nuclear import in postmitotic cardiomyocytes will provide findings important to the development of strategies for regenerating cardiomyocytes toward the development of an alternative therapeutic application (p 8, 1st column). Tamamori-Adachi differs from the claimed invention by not teaching the introduction of a gene encoding a factor that inhibits the production or function of Cip/kip family proteins into cardiomyocyte cultures.

However, at the time of the instant invention **Sutterluty et al,** teach $p45^{skp2}$ promotes $p27^{kip1}$ degradation and induces S phase in quiescent cells (title). Sutterluty et al teach the F-box protein $p45^{skp2}$ is the substrate-targeting subunit of the ubiquitin-protein ligase SCF^{SKP2} and expression of $p45^{skp2}$ in untransformed fibroblasts activates DNA synthesis in cells that would otherwise growth-arrest and expression of $p45^{skp2}$ induces quiescent fibrobalsts to enter S phase (p 207-209). Sutterluty et al, teach a vector for F-box protein $p45^{skp2}$ (p 214, under materials and methods). Sutterluty et al, teach that expression of $p45^{skp2}$ in quiescent fibroblasts promotes $p27^{Kip1}$ degradation, allows the generation of cyclin-A-dependent kinase activity and induces S phase (abstract). Sutterluty et al propose that $p45^{skp2}$ is important in the progression from quiescence to S phase and that the ability of $p45^{skp2}$ to promote $p27^{Kip1}$ degradation is a key aspect of its S-phase-inducing function abstract). Sutterluty et al teach **$p27^{Kip1}$ degradation, at the G1-to-S transition is critical for CDK2 activation** and the transition from quiescence to proliferation is the cyclin kinase inhibitors (CKI) $p27^{Kip1}$ and $p27^{Kip1}$ levels are high in quiescent cells but fall once cells enter the cell cycle (p 207, 1st column, 3rd

paragraph). Sherr et al, supplement the teachings of Sutterluty et al, by teaching that CDK inhibitors are positive and negative regulators of G1 to S phase transition in cells. Sherr et al teach that in the G1 phase of the cell cycle, cyclins and their corresponding kinases accumulate in the nucleus. For example cyclin D1 and CDK4 and CDK6 accumulate in the nucleus, phosphorylate retinoblastoma protein (Rb) causing its inactivation and sequester CDK inhibitors resulting in the progression of the cell cycle from G1 to S phase and CDK inhibitors such as $p27^{Kip1}$ negatively regulate cell cycle progression (p 1502, 1st column, and figure 1). Sherr et al teach that $p27^{Kip1}$ in proliferating cells is complexed to cyclin D-dependent kinases (p 1503, 1st column). In quiescent cells, the levels of $p27^{Kip1}$ are relatively high, whereas $p27^{Kip1}$ levels are low but usually increase in response to mitogenic signals during G1 phase progression (p 1503, 1st column). Titration of unbound p27Kip1 and $p27^{Kip1}$ molecules into higher order complexes with assembling cyclin D-dependent kinases relieves cyclin E–CDK2 from $p27^{Kip1}$ constraint, thereby facilitating cyclin E–CDK2 activation later in G1 phase (p 1503, 1st column). If Cip/Kip complexes cycle on and off cyclin E–CDK2, this could involve competition between accumulating cyclin D-dependent kinases and preassembled cyclin E–CDK2 for Cip/Kip proteins (p 1503, 1st column). The levels of untethered Cip/Kip proteins may also set an inhibitory threshold for activation of cyclin E–CDK2 and cyclin A–CDK2 synthesized later in G1 phase (p 1503, 1st column). Once the process of Cip/Kip sequestration lowers the effective CKI level to a critical point, cyclin E-CDK2 can facilitate its own activation by phosphorylating $p27^{Kip1}$ on a specific threonine residue (Thr-187) to trigger its degradation. Residual $p27^{Kip1}$ and p21Cip1 molecules remain bound to cyclin D–CDK complexes throughout subsequent cell cycles. This latent pool of tethered Cip/Kip proteins is released when mitogens are withdrawn and D cyclin synthesis stops, thereby inhibiting cyclin E–CDK2 and inducing G1 phase arrest, usually within a single cycle (p 1503, 1st column). In summary, Sherr et al teach that, in one,

cyclin D-dependent kinases phosphorylate Rb, contributing to its inactivation; in the other, cyclin D–CDK complexes act stoichiometrically to bind and sequester Cip/Kip proteins and the emergence of CDK2 activity during G1 requires inactivation of both the Cip/Kip proteins and Rb and is therefore dependent on prior activation of the cyclin D pathway (p 1503, 1st column lat paragraph bridge to 2nd column). Therefore, Sherr et al suggest that $p27^{Kip1}$ degradation is required for cells to progress through the late G1 phase into the S phase. Flink et al, teach that during terminal differentiation of cardiomyocytes p27 is increased (abstract) and Poolman et al, suggests that $p27^{Kip1}$ knock out mice resulted in a significant increase in heart size and in the total number of cardiac myocytes, thus loss of $p27^{Kip1}$ results in prolonged proliferation of the mouse cardiac myocytes (abstract). The combination of Sutterluty, Sherr, Flink and Poolman suggest the role of $p27^{Kip1}$ in cell cycle regulation for the cells to progress from the G1 to S phase and the role of $p27^{Kip1}$ in terminal differentiation of cardiomyocytes while its loss is associated with cardiomyocyte cell proliferation. As such the combination of Sutterluty, Sherr, Flink, and Poolman provide sufficient motivation for one of ordinary skill in the art to introduce a gene encoding a factor that inhibits the production or function of $p27^{kip1}$ to the cadiomyocyte system of Tamamori-Adachi in order to promote the progression of terminally differentiated cardiomyocytes through the G1 to S phase.

Accordingly, in view of the combination of the teachings of Sutterluty, Sherr, Flink, and Poolman, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to co-transfect with the Ad-D1NLS/ Ad-CDK4 the vector for F-box protein $p45^{skp2}$ to the cardiomyocyte cell culture system of Tamamori-Adachi in order to inhibit the production of the $p27^{kip1}$ gene in cultured cardiomyocytes with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification because Tamamori-Adachi et al teach that the nucleocytoplasmic transport of

cyclin D1 plays a critical role for determining proliferative capacity of cardiomyocytes and the mechanism preventing cyclin D1 nuclear accumulation remains unclear and suggest investigation of the molecular mechanism preventing cyclin D1 nuclear import in postmitotic cardiomyocytes will provide findings important to the development of strategies for regenerating cardiomyocytes toward the development of an alternative therapeutic application. One of ordinary skill in the art would have been sufficiently motivated to co-introduce the $p27^{kip1}$ inhibitor in terminally differentiated cardiomyocytes as Flink et al, teach that during terminal differentiation of cardiomyocytes p27 is increased taken with Poolman's suggestions that $p27^{Kip1}$ knock out mice resulted in a significant increase in heart size and in the total number of cardiac myocytes, thus loss of $p27^{Kip1}$ results in prolonged proliferation of the mouse cardiac myocytes.

Thus, the claimed invention as a whole is clearly prima facie obvious in the absence of evidence to the contrary.

Applicants argue that Adachi "differs from the claimed invention by not teaching the introduction of a gene encoding a factor that inhibits the production or function of Cip/Kip family proteins into cardiomyocyte cultures." Applicants argue that Adachi does not teach the introduction of a gene encoding a factor that inhibits the production, function or action of Cip/Kip family protein into cardiomyocytes.

These arguments are not persuasive in view of the new rejections where as discussed above in view of the combination of the teachings of Sutterluty, Sherr, Flink, Poolman, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to co-transfect with the Ad-D1NLS/ Ad-CDK4 the vector for F-box protein $p45^{skp2}$ to the cardiomyocyte cell culture system of Tamamori-Adachi in order to inhibit the production of the $p27^{kip1}$ gene in cultured cardiomyocytes. Tamamori-Adachi teaches a critical role of cyclin D1 nuclear import in cardiomyocyte proliferation and the combining teachings of Sutterluty, Sherr,

Flink, Poolman, teach the association of $p27^{Kip1}$ with cyclins and their corresponding kinases and the requirement for loss of $p27^{Kip1}$ in order for cardiomyocytes to progress through the G1 phase to the S phase of the cell cycle, therefore it would have been obvious to co-transfect with the Ad-D1NLS/ Ad-CDK4 the F-box protein $p45^{skp2}$ to a cardiomyocyte cell culture system to induce proliferation of adult cardiomyocytes.

Applicants argue that they have shown that the cell number of cardiomyocytes with the three genes namely D1NLS, CDK4 and Skp2 genes expressed therein was increased 5 fold or more as compared to cardiomyocytes infected with a control vector and cardiomyocytes infected with Ad-Skp2 alone.

These arguments are not persuasive in view of the combination of the teachings of Tamamori-Adachi, Sutterluty, Sherr, Flink, and Poolman to co-transfect with the Ad-D1NLS/ Ad-CDK4 the vector for F-box protein $p45^{skp2}$ to a cardiomyocyte cell culture system. Inherently, cardiomyocytes cotransfected with all three vectors will result in an increase of cell number as compared to control vector cardiomyocytes.

Applicants argue that Poolman does not directly prove the increase in the number of cardiomyocytes is due to the loss of the $p27^{Kip1}$ protein. At best, Poolman discloses that the loss of the $p27^{Kip1}$ gene in neonatal mice results in such an increase. The loss of the $p27^{Kip1}$ gene alone, however, is not sufficient for the efficient proliferation of cardiomyocytes.

These arguments are not persuasive in view of the combination of teachings where loss of $p27^{Kip1}$ is required in association with nuclear localization of G1 phase cell cyclins as taught by Sherr et al for the cells to progress through the cell cycle and divide. Sherr et al teach that, in one, cyclin D-dependent kinases phosphorylate Rb, contributing to its inactivation; in the other, cyclin D–CDK complexes act stoichiometrically to bind and sequester Cip/Kip proteins and the emergence of CDK2 activity during G1 requires inactivation of both the Cip/Kip proteins

and Rb and is therefore dependent on prior activation of the cyclin D pathway and therefore, $p27^{Kip1}$ degradation is required for cells to progress through the late G1 phase into the S phase. Therefore, Sherr et al suggest that $p27^{Kip1}$ degradation is required for cells to progress through the late G1 phase into the S phase, Flink et al, teach that during terminal differentiation of cardiomyocytes p27 is increased, and Poolman et al, suggests that $p27^{Kip1}$ knock out mice resulted in a significant increase in heart size and in the total number of cardiac myocytes, thus loss of $p27^{Kip1}$ results in prolonged proliferation of the mouse cardiac myocytes. Therefore, loss of the $p27^{Kip1}$ gene alone, is not sufficient for the efficient proliferation of cardiomyocytes as taught by the combined cited references.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2, 4-7, 16-21, 31 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 4, 18-19 of U.S. application 10/713,008 is withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 11, 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Magdalene K. Sgagias, Ph.D.
Art Unit 1632

PETER PARAS, JR.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600